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09/462,635	04/10/2000	GUNTER SCHMIDT	020600-285	5341

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EXAMINER

GOLDBERG, JEANINE ANNE

ART UNIT

PAPER NUMBER

1655

DATE MAILED: 12/21/2001

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/462,635

Applicant(s)

SCHMIDT ET AL.

Examiner

Jeanine A Goldberg

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on October 18, 2001.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 14-22, 42-49 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 14-22 and 42-49 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

- 13) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

- 15) ☐ Notice of References Cited (PTO-892)
- 16) ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
- 17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____
- 18) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 19) ☐ Notice of Informal Patent Application (PTO-152)
- 20) ☐ Other:

DETAILED ACTION

1. This action is in response to the papers filed October 18, 2001. Currently, claims 22, 42-49 are pending. All arguments have been thoroughly reviewed but are deemed non-persuasive for the reasons which follow.
2. Any objections and rejections not reiterated below are hereby withdrawn.
3. This action is FINAL.

Maintained Rejections

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

4. Claims 14-22, 42-46, 49-60, 63 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rothberg et al. (US Pat. 5,871,697, February 16, 1999) in view of Dynal Catalog (1995).

Rothberg et al (herein referred to as Rothberg) teaches a method for categorizing nucleic acid by

(i) digesting double-stranded nucleic acid with an endonuclease to produce a nucleic acid population, wherein the endonuclease is selected such that each nucleic

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acid in the resulting nucleic acid population has sticky ends of a known base sequence and of a known common length (col. 9, lines 42-43);

(ii) contacting the nucleic acid population with an adaptor to ligate the adaptor to a termini of each nucleic acid in the population such that the adaptor has a double stranded primer portion having a known base sequence and a single stranded portion complementary to the known sticky end of the nucleic acids of the population (col. 9, lines 43-56);

(iii) contacting the nucleic acid with one or more oligonucleotide sets (57-60) and

(iv) categorizing the nucleic acid by isolating nucleic acid which correctly hybridizes to an oligonucleotide set, wherein each oligonucleotide sequence in each oligonucleotide set has a pre-determined recognition sequence such that the recognition sequence is situated in the portion of the nucleic acid which was double stranded after digestion with the endonuclease (limitations of Claim 4, 7).

Simply, Rothberg teaches that following cDNA preparation, the next step is simultaneous RE cutting of and adapter ligation to the sample cDNA sequences (col. 48, lines 42-44). As seen in Figure 2D the oligonucleotide 222 comprises a segment complementary to the adaptor, the overhang/sticky end, the restriction endonuclease site and the double stranded nucleic acid (limitations of Claim 5, 8). Rothberg teaches that primers are preferably constructed with a subsequence 226 of P nucleotides. Length P is preferably from 1 to 6 and more preferably either 1 or 2 (col. 51, lines 49-56)(limitations of Claim 9, 10, 11). Rothberg teaches that if necessary, prior to the first step, the cDNA sample is prepared by methods commonly known in the art, such as

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amplification (col. 47, lines 23-26 and col. 87, lines 15-31)(limitations of Claim 12).

Rothberg teaches that the primer comprises at the 3' end of and contiguous with the longer strand sequence the portion of the restriction endonuclease recognition site remaining on the nucleic acid fragment terminus after digestion by the restriction endonuclease...contiguous to said one or more additional nucleotides, and optionally such that said primers comprising a particular said one or more additional nucleotides can be distinguishably detected from said primers comprising a different said one or more additional nucleotides (col. 11, lines 20-39). Rothberg teaches why a primer complementary to a portion of the double-stranded nucleic acid is preferable "the joint result of using primers 223 with subsequence 226 in multiple PCR reactions after one RE/ligase reaction is to extend the effective target subsequence from the RE recognition subsequence by concatenating onto the recognition sequence a subsequence which is complementary to subsequence 226 (limitations of Claim 37). Thereby, many additional target subsequences can be recognized while retaining the specificity and exactness characteristic of the RE embodiment (col. 52, lines 6-14). Rothberg explicitly teaches that restriction enzymes (RE's) such as those known as class IIS restriction enzymes, which produce overhangs of unknown sequence are less preferable (col. 41, lines 12-15). Rothberg teaches that preferred REs have a 6 bp recognition site and generate a 4 bp 5' overhang. The RE embodiments are also adaptable to a 2 bp 5' overhang, which is less preferred since 2 bp overhangs have a lower ligase substrate activity than 4 bp overhangs (col. 42, lines 5-9). Rothberg specifically teaches that adapter 250 is specific for the RE BamHI, as it has a 3' end

complementary to the 5' overhang generated by BamHI (col. 45, lines 64-65). Similarly, Adapter 251 is specific for HindIII.

Rothberg also teaches a kit which contains one or more restriction endonucleases, adapters and primers of the instant invention (col. 25-26)(limitations of Claim 26-29, 32-36). Rothberg teaches that the primers are detectably labeled such that primer with differing said one or two additional nucleotides have different labels that can be distinguishably detected (col. 26, lines 30-32).

Rothberg does not specifically teach categorizing the nucleic acid by denaturing the nucleic acid population, immobilizing the nucleic acids, extending the oligonucleotides, denaturing the double stranded nucleic acid, contacting the immobilized single stranded nucleic acid with a second set of oligonucleotide sequences, extending the oligonucleotide, denaturing and isolating the resulting non-immobilized nucleic acids.

However, Dynal teaches a method of generating and isolating non-immobilized single-stranded nucleic acid. Dynal teaches contacting a first set of oligonucleotide sequences, biotinylated primers, with the nucleic acid population. The single stranded primers hybridized, extended via PCR and then immobilized onto a Dynabead via the biotin (Figure 10.1) The double stranded nucleic acid is denatured and the non-biotinylated immobilized species is removed. The immobilized single-stranded nucleic acid is then contacted with a random priming or a specific labeled primer, a second set of oligonucleotide sequence, and extended to form a double-stranded nucleic acid. The

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double stranded nucleic acid is the denatured and the resulting non-immobilized single stranded nucleic acid is isolated.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Rothberg with the teachings of Dynal. The ordinary artisan would have been motivated to have performed the categorizing method of Rothberg and subsequently performed the method of Dynal to synthesize single-stranded probes in order to generate probes of known sequences in which were identified by the categorization method of Rothberg. Rothberg explicitly teaches that following the RE/ligase step is amplification of the doubly cut cDNA fragments such that any amplification method that selects fragments to be amplified based on end sequences is adaptable (col. 50, lines 5-8). The amplification method of Dynal is based upon the end sequences, thus would be considered an equivalent means of amplifying the cDNA fragments. The ordinary artisan would have been motivated to have amplified and generated nucleic acid from a sample for subsequent analysis in the categorization method. Moreover, it would be obvious to place these added reagents into the kit of Rothberg for the ability to easily perform the assay.

With regard to Claim 18, such that the oligonucleotide is contacted with the solid support prior to the nucleic acid population, it is well known that the primer may be contacted with the solid phase prior to the nucleic acid.

With regard to Claims 19-22, the teachings of Rothberg that oligonucleotides which has predetermined sequences of one or two bases would teach the ordinary

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artisan to use all of the possible combinations for the expected property of testing all possible combinations.

Response to Arguments

The response traverses the rejection. The response asserts that the method of the instant claims require that the nucleic acid population are categorized by isolating a nucleic acid wherein both termini of the double-stranded portion of the nucleic acid correctly hybridize to an oligonucleotide sequence. The response argues that neither of the references teach that both termini of the double stranded portion hybridize to an oligonucleotide sequence. This argument has been reviewed but is not convincing because Rothberg teaches "following the RE/ligase step is amplification of the doubly cut cDNA fragments. Although PCR protocols are described in the exemplary embodiments, any amplification method that selects fragments to be amplified based on end sequences is adaptable to this invention." (col. 50, lines 5-10). Since only double cut fragments are analyzed and ligated with an adaptor, the 5' and 3' end of the fragments would both contain the same adaptor sequence. Moreover, Rothberg clearly teaches using a primer as illustrated in Figure 2d for amplification. Rothberg teaches that the primer contains nucleotides which hybridize to the adaptor, the restriction enzyme overhang and nucleotides from the double stranded region following digestion with the restriction enzyme. The primer preferably contains either 1-2 nucleotides from the double stranded region. Rothberg teaches mixing the four possible primers in four separate aliquots for use with one of the four primers such that the four reactions will select for amplification only one of the possible dsDNAs. Thus, Rothberg teaches

single primer PCR using the same primer such that in the event that the primer matches on both termini, the amplification will exist. Rothberg therefore teaches identifying both ends of the nucleic acid.

Moreover, the response asserts that the ordinary artisan would not be motivated to combine the references. The response asserts that the ordinary artisan would not have arrived at the invention as claimed by simply performing the method of Rothberg followed by the method of Dynal. This argument has been reviewed but is not convincing because Rothberg clearly teaches that any amplification method is adaptable to this invention. Dynal teaches a method of amplification by biotinylating a primer and amplifying the probe template followed by capture and subsequent extension using a specific labeled primer. Thus, to biotinylate a primer which contains 1-2 nucleotides from the double stranded region, as taught by Rothberg, would meet the limitations of the claims. The ordinary artisan would be motivated to have used the method of Dynal to further label the identified probes for isolation and detection.

The response also argues that the Dynal catalog does not relate to a method of amplifying DNA, but relates to a method of producing labeled single-stranded probes from double stranded DNA. This argument has been reviewed but is not convincing because the first step of the Dynal method requires amplification of a biotinylated primer. Thus, Dynal clearly is related to amplifying DNA. Moreover, extension is used later in the method for extending a specific labeled primer. Each of these steps are related to amplifying DNA to obtain a labeled probe.

Thus for the reasons above and those already of record, the rejection is maintained.

5. Claims 47-48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rothberg et al. (US Pat. 5,871,697, February 16, 1999 or Rothberg et al. (US Pat. 5,871,697, February 16, 1999) in view of Dynal Catalog (1995) as applied to Claims 14-22, 42-46, 49-60, 63 above, and further in view of Hartley et al (US Pat 5,106,727, April 1992).

Rothberg et al (herein referred to as Rothberg) teaches a method for categorizing nucleic acid by

(i) digesting double-stranded nucleic acid with an endonuclease to produce a nucleic acid population, wherein the endonuclease is selected such that each nucleic acid in the resulting nucleic acid population has sticky ends of a known base sequence and of a known common length (col. 9, lines 42-43);

(ii) contacting the nucleic acid population with an adaptor to ligate the adaptor to a termini of each nucleic acid in the population such that the adaptor has a double stranded primer portion having a known base sequence and a single stranded portion complementary to the known sticky end of the nucleic acids of the population (col. 9, lines 43-56);

(iii) contacting the nucleic acid with one or more oligonucleotide sets (57-60) and

(iv) categorizing the nucleic acid by isolating nucleic acid which correctly hybridizes to an oligonucleotide set, wherein each oligonucleotide sequence in each

oligonucleotide set has a pre-determined recognition sequence such that the recognition sequence is situated in the portion of the nucleic acid which was double stranded after digestion with the endonuclease (limitations of Claim 4, 7).

Simply, Rothberg teaches that following cDNA preparation, the next step is simultaneous RE cutting of and adapter ligation to the sample cDNA sequences (col. 48, lines 42-44). As seen in Figure 2D the oligonucleotide 222 comprises a segment complementary to the adaptor, the overhang/sticky end, the restriction endonuclease site and the double stranded nucleic acid (limitations of Claim 5, 8). Rothberg teaches that primers are preferably constructed with a subsequence 226 of P nucleotides. Length P is preferably from 1 to 6 and more preferably either 1 or 2 (col. 51, lines 49-56)(limitations of Claim 9, 10, 11). Rothberg teaches that if necessary, prior to the first step, the cDNA sample is prepared by methods commonly known in the art, such as amplification (col. 47, lines 23-26 and col. 87, lines 15-31)(limitations of Claim 12). Rothberg teaches that the primer comprises at the 3' end of and contiguous with the longer strand sequence the portion of the restriction endonuclease recognition site remaining on the nucleic acid fragment terminus after digestion by the restriction endonuclease...contiguous to said one or more additional nucleotides, and optionally such that said primers comprising a particular said one or more additional nucleotides can be distinguishably detected from said primers comprising a different said one or more additional nucleotides (col. 11, lines 20-39). Rothberg teaches why a primer complementary to a portion of the double-stranded nucleic acid is preferable "the joint result of using primers 223 with subsequence 226 in multiple PCR reactions after one

RE/ligase reaction is to extend the effective target subsequence from the RE recognition subsequence by concatenating onto the recognition sequence a subsequence which is complementary to subsequence 226 (limitations of Claim 37). Thereby, many additional target subsequences can be recognized while retaining the specificity and exactness characteristic of the RE embodiment (col. 52, lines 6-14). Rothberg explicitly teaches that restriction enzymes (RE's) such as those known as class IIS restriction enzymes, which produce overhangs of unknown sequence are less preferable (col. 41, lines 12-15). Rothberg teaches that preferred REs have a 6 bp recognition site and generate a 4 bp 5' overhang. The RE embodiments are also adaptable to a 2 bp 5' overhang, which is less preferred since 2 bp overhangs have a lower ligase substrate activity than 4 bp overhangs (col. 42, lines 5-9). Rothberg specifically teaches that adapter 250 is specific for the RE BamHI, as it has a 3' end complementary to the 5' overhang generated by BamHI (col. 45, lines 64-65). Similarly, Adapter 251 is specific for HindIII.

Rothberg also teaches a kit which contains one or more restriction endonucleases, adapters and primers of the instant invention (col. 25-26)(limitations of Claim 26-29, 32-36). Rothberg teaches that the primers are detectably labeled such that primer with differing said one or two additional nucleotides have different labels that can be distinguishably detected (col. 26, lines 30-32).

Rothberg does not specifically teach the incorporation of analogues into the oligonucleotides.

However, Hartley et al. (herein referred to as Hartley) teaches incorporating non-standard bases into random primers to reduce de novo synthesis.

Therefore, it would have been **prima facie** obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Rothberg to include the non-standard bases as taught by Hartley for reducing the de novo synthesis. The ordinary artisan would have been motivated to have reduced the amount of de novo synthesis to obtain results representative of the categorized population as opposed to additional nucleic acid molecules.

Response to Arguments

The response traverses the rejection. The response asserts that Hartley does not solve the deficiencies of Rothberg and Dynal. However, as provided above, Rothberg and Dynal obviate the instant method. Thus for the reasons above and those already of record, the rejection is maintained.

Conclusion

6. **No claims allowable over the art.**
7. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the

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shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Enewold Goldberg whose telephone number is (703) 306-5817. The examiner can normally be reached Monday-Thursday from 7:00AM to 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax number for this Group is (703) 305- 3014.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Jeanine Enewold Goldberg
December 20, 2001



JEFFREY FREDMAN
PRIMARY EXAMINER